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**SOLID DISPERSED PREPARATION OF POORLY WATER-SOLUBLE DRUG  
CONTAINING OIL, FATTY ACID OR MIXTURES THEREOF**

Abstract:

Disclosed is a solid dispersed preparation for poorly water-soluble drugs, which is prepared by dissolving or dispersing the poorly water-soluble drugs in an oil, a fatty acid or a mixture thereof, mixing the solution or dispersion in a water-soluble polyol matrix and drying the mixture. The solid dispersed preparation can be formulated into a power formulation or a granule formulation. The solid dispersed preparation is improved in the solubility of poorly water-soluble drugs in the gastro-intestinal tract, resulting in a great increase in the bioavailability of the drugs. In addition, the solid dispersed preparation gives the pharmaceutical solutions to the problems that the conventional semi-solid or liquid preparations possess, enabling medicinally effective, poorly water-soluble compounds to be formulated, molded and processed, quickly and in an economically favorable manner without use of any organic solvent.

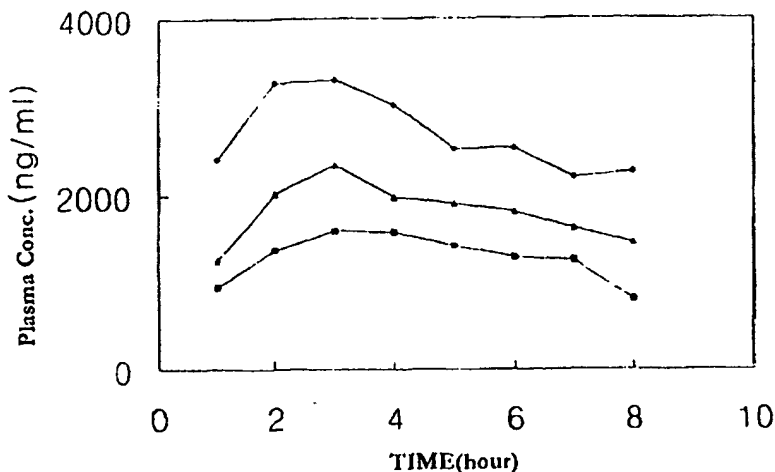
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Disclosed is a solid dispersed preparation for poorly water-soluble drugs, which is prepared by dissolving or dispersing the poorly water-soluble drugs in an oil, a fatty acid or a mixture thereof, mixing the solution or dispersion in a water-soluble polyol matrix and drying the mixture. The solid dispersed preparation can be formulated into a power formulation or a granule formulation. The solid dispersed preparation is improved in the solubility of poorly water-soluble drugs in the gastro-intestinal tract, resulting in a great increase in the bioavailability of the drugs. In addition, the solid dispersed preparation gives the pharmaceutical solutions to the problems that the conventional semi-solid or liquid preparations possess, enabling medicinally effective, poorly water-soluble compounds to be formulated, molded and processed, quickly and in an economically favorable manner without use of any organic solvent.

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SOLID DISPERSED PREPARATION OF POORLY WATER-SOLUBLE DRUG  
CONTAINING OIL, FATTY ACID OR MIXTURES THEREOF

BACKGROUND OF THE INVENTION

5

Field of the Invention

The present invention relates to a solid dispersed preparation for poorly water-soluble drugs or biologically active substances. More particularly, this invention  
10 relates to a solid dispersed preparation which allows poorly water-soluble drugs to be increased in the uptake efficiency in the gastro-intestinal track and is convenient to make in a pharmaceutical formulation.

15 Description of the Prior Art

A good many drugs poorly dissolve in water. When being administered to a body, these poorly water-soluble drugs have so low solubility and releasing rate in digestive juices as to retard their absorption, resulting the  
20 bioavailability decreased. In order to solve this problem, various preparation methods were developed with the aim of solubilizing these poorly water-soluble drugs and increasing their releasing rates. For instance, there have been reported many methods for improving the  
25 bioavailability of drugs, including micronization, formation of micelles by use of surfactant, solvent deposition, utilization of dry elixirs, co-precipitation

by use of inert water-soluble carriers, solid-dispersion and formation of inclusion complexes using cyclodextrins.

In conducting these methods, however, the drugs to be administered do not show a constant increase in solubility.

5 Thus, they are problematic in terms of preparation, commercialization, and efficiency.

For the poorly water-soluble drugs, which are also poor in internal uptake, there have been made attempts to enhance their bioavailability upon administration.

10 However, the dosage forms developed thus far, are of semi-solid or liquid form, giving disadvantages in pharmaceuticals, especially in formulating, molding and processing.

## 15 SUMMARY OF THE INVENTION

We, the inventors made the intensive and thorough research on the formulation of poorly water-soluble drugs, to improve the bioavailability of the drugs upon  
20 administration. As a result, we found that the dispersion or solution of the poorly water-soluble drugs in oils, fatty acids or mixtures thereof, followed by mixing with a water-soluble polymer matrix allowed the drugs to efficiently release in the gastro-intestinal tract and the  
25 mixture can be formed into a solid form.

Therefore, it is an object of the present invention to provide a solid dispersed preparation which improves the

bioavailability of poorly water-soluble drugs by enhancing the release of the drugs in the gastro-intestinal tract.

It is another object of the present invention to provide a solid dispersed preparation which can be prepared by simple and convenient process with an economical benefit.

According to the present invention, a solid dispersed preparation for poorly water-soluble drugs is prepared by dissolving or dispersing the drugs in an oil, a fatty acid or a mixture thereof, mixing the solution or dispersion in a water-soluble polyol matrix and drying the mixture.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**Fig. 1** is a graph in which the plasma concentration of cyclosporine is plotted against the times after administrating the solid dispersed preparations of the present invention (closed rectangle and closed triangle) and a commercially available preparation (Neoral, closed lozenge);

**Fig. 2** is a graph in which the plasma concentration of aceclofenac is plotted against the times after orally administrating aceclofenac powder (closed circle) and the solid dispersed preparation of the present invention (open circle, oleic acid 5%) to rats;

**Fig. 3** is a graph in which the plasma concentration of cyclosporine is plotted against the times after

administering the solid dispersed preparation of the present invention (closed circle, capsule containing 100 mg of the preparation) and a commercially available preparation (open circle, Airtal capsule 100 mg) to beagle dogs;

**Fig. 4** is a graph in which the plasma concentration of aceclofenac is plotted against the times after orally administering the solid dispersed preparation of the present invention (closed circle, capsule containing 100 mg of the preparation) and a commercially available preparation (open circle, Airtal capsule 100 mg) to humans; and

**Fig. 5** is a graph in which the plasma concentration of cisapride is plotted against the times after orally administering the solid granular preparations of the present invention (open circle, bead 10 mg) and a commercially available preparation (closed circle, prepulsid 10 mg) to humans.

## 20 DETAILED DESCRIPTION OF THE INVENTION

Hereinafter, the present invention will be described in detail.

In accordance with the present invention, there is provided a solid dispersed preparation for poorly water-soluble drugs, which is prepared by dispersing or dissolving the drugs in an oil, a fatty acid or a mixture

thereof, incorporating the dispersion or solution into a water-soluble polymer matrix and drying this mixture.

In particular, this invention provides two types of fomulation, i.e., the solid powdery preparation and the  
5 solid granular preparation.

The preparation method of the solid dispersed powders comprises the following steps; Dissolving or dispersing the poorly water-soluble drugs in an oil, a fatty acid or the mixture thereof; mixing with the water-soluble polymer  
10 matrix; drying the mixture; and grinding the pellet into powders.

In addition, the preparation method of the solid dispersed granules comprises the following steps;  
Dissolving or dispersing the poorly water-soluble drugs in  
15 an oil, a fatty acid or the mixture thereof; mixing with the water-soluble polymer matrix; spraying onto a pharmaceutically acceptable nucleus, resulting the granules. In a preferred embodiment, the pharmaceutically acceptable nucleus may be a sugar sphere.

20 The solid dispersed powdery preparation or the solid dispersed granular preparation of this invention can be formulated into the pharmaceutically acceptable medicines for internal use such as powders, granules, tablets and capsules.

25 Hereinafter, the word "solid dispersed preparation" means "solid dispersed powdery preparation", "solid dispersed granular preparation" or the both.



In this regard, the oil, the fatty acid or the mixture thereof may be used alone or in a form of an emulsion or microemulsion inclusive of itself. When dispersing or dissolving poorly water-soluble drugs in the oil, fatty acid or mixture thereof, a surfactant may be added together.

Further, the water-soluble polymer matrix may be used alone or in combination with another water-soluble matrix.

Illustrative examples of the oil that can be used in the preparation of the present invention include lipid additives, such as  $\alpha$ -bisabolol, stearyl glycerphosphate, salicylic acid, tocopheryl acetate, a mixture of water, alcohol and Perilla extract, sodium hyaluronate, panthenol, propylene glycol and apple (*Pirus Malus*), propylene glycol and pineapple, ivy (*Hedera halix*) extract and 1,3-B.G, peach (*Prums persica*) leaf extract, hydrolyzed soy flour, wheat (*Triticum Vulgare*) protein, birch (*Betula alba*) extract and 1,3-B.G, burdock (*Arctium majus*) extract and 1,3-B.G; liposomes; phosphatidylcholines; esters, such as glyceryl stearate, captylic/capric triglyceride, cetyl octanoate, isopropyl myristate, 2-ethylene isopelagonate, di-C12-13 alkyl malate, ceteatyl octanoate, butylene glycol dicaptylate/dicaprate, isononyl isostearate, isostearyl isostearate, coco-captylate/caprate, cetyl octanoate, octyldodecyl myristate, cetyl esters, C10-30 cholesterol/lanosterol ester, hydrogenated castor oil, monoglycerides, diglycerides, and triglycerides; hydrocarbons, such as beeswax, canauba wax, sucrose

distearate, PEG-8 beeswax and candelilla (*euphorbia cerifera*) wax; mineral oils such as ceresin and ozokerite; vegetable oils such as macadamia ternifolia nut oil, hydrogenated hi-erucic acid rape seed oil, olive oil, jojoba oil, hybridsunflower (*Helianthus annuus*) oil, neem (*melia azadirachta*) seed oil, dog rose (*rosa canina*) lips oil with preference to mineral oils, squalene, squalane, monoglycerides, diglycerides, triglycerides, medium-chain glyceride, myglyol, cremophor, hydrogenated castor oil, corn oil, Perilla oil, cotton seed oil and lipid-soluble vitamins.

As for the fatty acid, it is preferable to use oleic acid, cetyl alcohol, stearyl alcohol, stearic acid, myristic acid, linoleic acid or lauric acid. More preferable is to use oleic acid, linoleic acid, or isopropyl myristate.

As the water-soluble matrix, polyethylene glycol (PEG), carbowax or polyvinyl pyrrolidone (PVP) is available. Aforementioned water-soluble matrix may be used in combination with other matrixes, examples of which include water-soluble matrices such as gelatin, gum, carbohydrates, celluloses, polyvinyl alcohol, polyacrylic acid, inorganic compounds and mixtures thereof; and enteric matrices such as hydroxypropylmethylcellulose acetyl succinate (HPMCAS), cellulose acetate phthalate, shellac, zein, polyvinyl acetate phthalate, Eudragit L100, Eudragit S100, sodium arginate and poly-L-lysine.

In order to enhance the dispersion or dissolution of poorly water-soluble drugs in the oil, fatty acid or their mixture, a surfactant may be added, which is selected from the group comprising glyceryl stearate, polysorbate 60, polysorbate 80, sorbitan trioleate, sorbitan sesquioleate, sorbitan stearate, PEG-20 glyceryl isostearate, ceteth-25, PEG-60 hydrogenated castor oil, nonoxynol-15, PEG-6-decyltetradeceth-20, dimethicone copolyol, glyceryl diisostearate, ceteth-24, cetearyl alcohol, polyoxyethylene nonyphenyl ether, PEG-40 hydrogenated castor oil, cetyl dimethicone copolyol, polyglyceryl-3-methylglucose distearate, PEG-100 stearate, sorbitan isostearate, sodium lauryl glutamate, disodium cocoamphodiacetate, lauric acid diethanolamide, coconut fatty acid diethanolamide, N,N-bis-(2-hydroxy ethyl)-cocomide, and cocoamidopropyl betain.

The solid dispersed preparation of the present invention can be applied for all the poorly water-soluble drugs and preferably for ketoconazole; itraconazole and its derivatives; cyclosporine; cisapride; acetaminophen; aspirin; acetylsalicylic acid; indomethacin; naproxen; warfarin; papaverine; thiabendazole; miconazole; cinnarizine; doxorubicin; omeprazole; cholecalciferol; melphalan; nifedipine; digoxin; benzoic acid; tryptophan; tyrosine; phenylalanine; aztreonam; ibuprofen; phenoxymethylpenicillin; thalidomide; methyltestosterone; prochlorperazine; hydrocortisone; dideoxypurine

nucleoside; vitamin D<sub>2</sub>; sulfonamide; sulfonylurea; p-aminobenzoic acid; melatonin; benzylpenicillin; chlorambucil; diazepam; digitoxin; hydrocortisone butyrate; metronidazole benzoate; tolbutamide; 5 prostaglandin E<sub>1</sub>(PGE<sub>1</sub>); fludrocortisone; griseofulvin; miconazole nitrate; leukotriene B<sub>4</sub> antagonist; propranolol; theophylline; flubiprofen; sodium benzoate; benzoic acid; riboflavin; benzodiazepine; phenobarbital; glyburide; sulfadiazine; sulfaethylthiadiazole; sodium 10 diclofenac; aceclofenac; phenyroin; hioridazinehydrochloride; bropirimine; hydrochlorothiazide; fluconazole; acyclovir; bucillamine; ciprofluoxacin; acetyl-L-carnitine; baclofen; sodium alendronate; lovocarnitine; nimodipine or nimodifine; 15 atenolol; provastatin sodium; lovastatin; isotretinoin; etidronate disodium; doxifluridine; fosfomycin calcium; sotepine; epinastine hydrochloride; carvedilol; epinastine hydrochloride; carvedilol; fosinopril; trandolapril; etretinate cap; metergoline; 20 mercaptopurine; vancomycin hydrochloride; cefixime; cefuroxim axetil; dirithramycin; and dadanosin and more preferably for ketoconazole, itraconazole and its derivatives, cisapride, cyclosporine and nifedipine.

Over conventional methods, the present invention has 25 an advantage, in that, the solid dispersed preparation can be prepared with ease and show high efficiency in absorption and release.

First, a poorly water-soluble medicine is homogeneously mixed and dispersed in an oil, fatty acid or their mixture and added in water-soluble polymer matrices molten at room temperature or about 60-80 °C, after which the  
5 resulting mixture is cooled rapidly to room temperature and dried in an oven for 12 hours or more. The dried pellet is powdered in a mortar and passed through a sieve to give powder which is uniform in particle size. As  
aforementioned, when the drug is dispersed or dissolved in  
10 the oil, fatty acid or their mixture, the oil, fatty acid or their mixture may be emulsified or micro-emulsified. In this case, a surfactant may be added to the solution.

Alternatively, after the homogeneous dispersion of the poorly water-soluble drug is added in the water-soluble  
15 polymer matrix molten at about 60-80 °C, it may be sprayed to pharmaceutically acceptable nucleus to give a granule.

As a consequence of an examination which was made on the solubility of the solid dispersed preparation in distilled water, artificial intestinal juice and  
20 artificial gastric juice, the solubility of the solid dispersed preparation is found to be better than those of poorly water-soluble drugs themselves. Particularly, a great advance can be brought into the solubility of poorly water-soluble drugs when they are incorporated into a solid  
25 dispersed preparation containing oleic acid or micro-emulsified oleic acid.

The data obtained from the experiments in which the

solid dispersed preparations of the present invention are eluted in artificial gastric juice and artificial intestinal juice, show that the solid dispersed preparations of the present invention are superior to the  
5 poorly water-soluble drugs themselves in releasing rate.

A significant improvement in releasing rate is observed when a solid dispersed preparation containing oleic acid or microemulsified oleic acid is used. In the artificial intestinal juice, a severer condition in which for drugs to  
10 dissolve, rather than in the artificial gastric juice, the improvement in the releasing rate by virtue of the solid dispersed preparation is more apparent.

Through an experiment which is conducted for examining the uptake efficiency of poorly water-soluble drugs in the  
15 gastro-intestinal tract, the superiority of the solid dispersed preparation according to the present invention is also demonstrated. Even when only a water-soluble matrix is used, the uptake efficiency of the drugs is minutely increased. In particular, the uptake efficiency of drugs  
20 in the gastro-intestinal tract is remarkably improved when they are incorporated in a solid dispersed preparation using oleic acid-containing microemulsions.

In addition, comparison of the plasma concentration of target drug molecule after oral administration between the  
25 solid dispersed preparation and conventional preparations, is helpful in understanding the present invention. As a result, similar levels are observed, suggesting that the

solid dispersed preparation of the present invention can substitute for conventional preparations when account is taken of pharmaceutical aspects.

A better understanding of the present invention may be obtained in light of the following examples which are set forth to illustrate, but are not to be construed to limit the present invention.

Following are the compositions of emulsions and microemulsions used in Examples.

10

**EMULSIONS****PREPARATION EXAMPLE I**

15	Waxes	Composition (%)
	KALCHOL 6870	1.800
	EMERSOL 132	1.000
	Multi-Wax W-445	1.700
20	Emulsifiers	
	ATLAS G-144	1.800
	ATLAS G-610	1.900
	ATMOS 370	0.800
	KM-105	2.000
25	Oils	
	CRODALAN SWL	1.500

	LEXOL GT 865	4.000
	NIKKOL CIO	4.000
	SEPERIOR JOJOBA OIL	1.000
	SF 1202	0.200
5	KF-96(100CS)	0.300
	DRAKEOL 7	5.000
	Squalane	2.000
	dl-a-Tocopheryl Acetate	0.100
	POLYOLPERPOLYMER-2	0.200
10		
	Aqueous Phase	
	DI-WATER	60.852
	glycerin	2.000
	P.G	7.000
15	NATURAL EXT.AP	0.500
	LUBRAGEL CG	0.200
	Carbopo 1940	0.100
	KELTROL F	0.020
	NaOH	0.028
20		

**PREPARATION EXAMPLE II**

	Waxes	
	KALCHOL 6870	1.800
25	EMERSOL 132	1.000
	Multi-wax W-445	1.700



## Emulsifiers

	RHEODOL AO-15	0.800
	RHEODOL MS-162	2.000
	RHEODOL TW-S120	1.900
5	KM-105	2.000

## Oils

	CRODALAN SWL	1.500
	LEXOL GT 865	5.000
10	NIKKOL CIO	2.500
	Macadamia ternifolia nut oil	1.000
	SF 1202	0.300
	KF-96(100CS)	0.300
	DRAKEOL 7	7.000
15	Squalane	0.500
	dl-a-Tocopheryl Acetate	0.100
	POLYOLPERPOLYMER-2	0.100

## Aqueous phase

20	DI-WATER	61.780
	glycerin	2.000
	1.3-B.G	6.000
	NATURAL EXT.AP	0.300
	LUBRAGEL CG	0.200
25	Carbopol 940	0.100
	KELTROL F	0.020
	TEA	0.100

## PREPARATION EXAMPLE III

## Waxes

	KALCHOL 6870	0.500
5	EMERSOL 132	0.500
	Beeswax	0.400

## Emulsifiers

	ATLAS G-114	2.200
10	ATLAS G-610	0.800
	ATMOS 370	0.800
	KM-105	0.700

## Oils

15	CRODALAN SWL	0.500
	LEXOL GT 865	3.000
	NIKKOL CIO	3.000
	SUPERIOR JOJOGA OIL	0.500
	SR 1202	0.200
20	KF-96(100CS)	0.100
	DRAKEOL 7	3.000
	Squalane	0.500
	dl-a-Tocopheryl Acetate	0.100
	POLYOLPERPOLYMER-2	0.200

25

## Aqueous phase

	DI-WATER	74.146
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	Glycerin	2.000
	P.G	6.000
	NATURAL EXT.AP	0.500
	LUBRAGEL CG	0.200
5	Carbopol 940	0.100
	KELTROL F	0.020
	NaOH	0.0336

**PREPARATION EXAMPLE IV**

10

## Waxes

	KALCHOL 6870	0.400
	EMERSOL 132	0.500
	Multi-Wax W-445	0.400

15

## Emulsifiers

	RHEODOL AO-15	0.800
	RHEODOL MS-165	2.200
	RHEODOL TW-S120	0.800
20	KM-105	0.600

## Oils

	CRODALAN SWL	0.500
	LEXOL GT 865	3.000
25	NIKKOL CIO	2.000
	Macadamia ternifolia nut oil	1.000
	SF 1202	0.400

	DRAKEOL 7	4.500
	Squalane	0.500
	dl-a-tocopheryl acetate	0.100
	POLYOLPERPOLYMER-2	0.100
5		
	Aqueous phase	
	DI-WATER	73.480
	glycerin	2.000
	1,3-B.G	6.000
10	NATURAL EXT.AP	0.300
	LUBRAGEL CG	0.200
	Cabopol	0.100
	KELTROL F	0.020
	TEA	0.100

15

**MICROEMULSIONS****PREPARATION EXAMPLE V**

20 Waxes

Cetyl Alcohol	3.000
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Emulsifiers

	NIKKOL HCO-60	5.000
25	RHEODOL TW-0120	5.000
	Cremophor EL	20.000

## Oils

I.P.M	5.000
CAPTEX	5.000

## 5 Aqueous phase

DI-WATER	52.000
Ethanol	5.000

## PREPARATION EXAMPLE VI

10

## Emulsifiers

NIKKOL HCO-60	5.000
RHEODOL TW-0120	5.000
Cremophor EL	5.000

15

## Oils

I.P.M	5.000
Lanolin oil	5.000
CAPTEX	5.000

20

## Aqueous phase

DI-WATER	50.000
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## PREPARATION EXAMPLE VII

25

## Surfactant

LABRASOL	15.000
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	Surfactant Aid	
	Polyglyceryl oleate	5.000
	PLURL OLEIQUE	5.000
5	Oil phase	
	LABRAFIL M1994CS	4.500
	Sub-Solvent	
10	Transcutol	5.000
	Aqueous phase	
	Phosphate buffer(pH 6)	64.500

15 **PREPARATION EXAMPLE VIII**

	Oil phase	
	GELUCIRE 44/14	11.429
	GELUCIRE 48/09	11.429
20	Surfactant	
	LABRAFAC CM 10	10.714
	Surfactant Aid	
	LAUROGLYCOL	7.143
25	Transcutol	59.285

**PREPARATION EXAMPLE IX**

## Aqueous Phase

	Water (Buffer)	57,050
	Physiological Saline Solution	4,000
5	Glucose	1,000
	Propylene Glycol PEG 300,400	5,000
	Glycerol	5,000

## Oil Phase

10	Fatty Acid Esters	5,000
	Modified Vegetable Oil	0.500
	Silicon Oil	0.500

## Surfactant Aid

15	Long Chain Alcohol	3,750
	Glycol Derivative	2,500
	Propylene Glycol Derivative	1,200
	Polyglycerol Derivative	4,500

## 20 Surfactant

	Non-ionic Surfactant	10,000
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## PREPARATION EXAMPLE X

## 25 Oil Phase

	Oleic Acid	6,250
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	Surfactant	
	Tween 80	12,500
	Surfactant Aid	
5	Transcutol	8,750
	Aqueous Phase	
	Water	72,500

10                   **PREPARATION EXAMPLE XI**

	Oil Phase	
	Captex	5,000
15	Surfactant	
	Cremophor	12,500
	Surfactant Aid	
	Transcutol	6,250
20	Aqueous Phase	
	Water	76,250

**COMPARATIVE EXAMPLE I**

25

After being melted at about 70 °C, 90 g of PEG 6000 was added with 10 g of ketoconazole, cooled rapidly to room



temperature and dried in an oven for 12 hours or more.

The dried solid dispersed preparation was milled in a mortar and passed through a sieve to give a powder which was uniform in particle size.

5

#### EXAMPLE I

In 5 g of oleic acid were homogeneously mixed and dispersed 10 g of ketoconazole which was, then, added into  
10 85 g of PEG 6000 which was molten at about 70 °C. After being cooled rapidly to room temperature and dried in an oven for 12 hours or more, the dried solid dispersed preparation was milled in a mortar and passed through a sieve to give a powder which was uniform in particular size.

15

#### EXAMPLE II

In 5 g of oleic acid and 5 g of Tween 80 were homogeneously mixed and dispersed 10 g of ketoconazole  
20 which was, then, added in 80 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

25

#### EXAMPLE III

In 5 g of isopropyl myristate was homogeneously mixed

and dispersed 10 g of ketoconazole which was, then, added in 80 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

5

#### EXAMPLE IV

In 5 g of liquid paraffin was homogeneously mixed and dispersed 10 g of ketoconazole which was, then, added in 80 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE V

15

In 5 g of cremophor was homogeneously mixed and dispersed 10 g of ketoconazole which was, then, added in 80 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE VI

In 5 g of cremophor and 5 g of Tween 80 was homogeneously mixed and dispersed 10 g of ketoconazole which was, then, added in 80 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was

obtained in the same procedure as in Example I.

#### EXAMPLE VII

5        In 5 g of isopropyl myristate and 5 g of Tween 80 was  
homogeneously mixed and dispersed 10 g of ketoconazole  
which was, then, added in 80 g of PEG 6000 which was molten  
at about 70 °C. Using this mixture, a dispersed powdery  
preparation was obtained in the same procedure as in Example  
10 I.

#### EXAMPLE VIII

15        In 5 g of liquid paraffin and 5 g of Tween 80 was  
homogeneously mixed and dispersed 10 g of ketoconazole  
which was, then, added in 80 g of PEG 6000 which was molten  
at about 70 °C. Using this mixture, a dispersed powdery  
preparation was obtained in the same procedure as in Example  
I.

20

#### EXAMPLE IX

25        In a microemulsion containing 5 g of cremophor, 5 g of  
oleic acid, 35 g of alcohol and 1 g of transcitol was  
homogeneously dissolved and dispersed 10 g of ketoconazole,  
followed by evaporating the alcohol. The solid residue was,  
then, added in 43 g of PEG 6000 molten at about 70 °C.

Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE X

5

In a microemulsion containing 5 g of cremophor, 5 g of oleic acid and 1 g of transcitol was dissolved 10 g of ketoconazole which was, then, dispersed in 35 g of distilled water, followed by evaporating the distilled water in an oven. The solid residue was added in 43 g of PEG 6000 molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

15

#### EXAMPLE XI

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of ketoconazole. 40 g of hydroxypropylmethylcellulose, an enteric matrix, was added in 40 g of PEG 6000 molten at 70 °C. Using the mixture of the above two solutions, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE XII

25

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of itraconazole which was, then, added in 80

g of PEG 6000 which was molten at 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

5

**EXAMPLE XIII**

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of itraconazole. 40 g of hydroxypropylmethylcellulose, an enteric matrix, was added  
10 in 40 g of PEG 6000 which was molten at 70 °C. Using the mixture of the above two solutions, a dispersed powdery preparation was obtained in the same procedure as in Example I.

15

**EXAMPLE XIV**

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of an itraconazole derivative (Dong-A Pharmacy Co., Ltd., Korea) which was, then, added in 80 g  
20 of PEG 6000 which was molten at 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

25

**EXAMPLE XV**

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of cyclosporine which was, then, added in 80

g of PEG 6000 which was molten at 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

5

**EXAMPLE XVI**

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of cyclosporine. 40 g of hydroxypropylmethylcellulose, an enteric matrix, was added in 40 g of PEG 6000 which was molten at 70 °C. Using the mixture of the above two solutions, a dispersed powdery preparation was obtained in the same procedure as in Example I.

15

**EXAMPLE XVII**

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of cisapride which was, then, added in 80 g of PEG 6000 which was molten at 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

25

**EXAMPLE XVIII**

In 5 g of oleic acid and 5 g of Tween 80 was homogeneously mixed and dispersed 10 g of cisapride which was, then, added in 80 g of PEG 6000 which was molten at 70

°C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE XIX

5

In a microemulsion containing 10 g of cremophor, 5 g of oleic acid and 7 g of transcitol was homogeneously dissolved and dispersed 10 g of itraconazole, followed by evaporating the alcohol in an oven. The solid residue was, then, added in 43 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE XX

15

In a microemulsion containing 10 g of cremophor, 4 g of captex and 5 g of transcitol was homogeneously dissolved and dispersed 10 g of cyclosporine, followed by evaporating the alcohol in an oven. The solid residue was, then, added in 43 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE XXI

25

In a microemulsion containing 10 g of cremophor, 5 g of oleic acid and 7 g of transcitol was homogeneously

dissolved and dispersed 10 g of cisapride, followed by evaporating the alcohol in an oven. The solid residue was, then, added in 43 g of PEG 6000 which was molten at about 70 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE XXII

In 5 g of oleic acid was homogeneously mixed and dispersed 10 g of ketoconazole which was, then, added in 80 g of molten PVP. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### EXAMPLE XXIII

In a microemulsion containing 5 g of oleic acid was homogeneously mixed and dispersed 10 g of ketoconazole which was, then, added in 80 g of molten PVP. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example I.

#### COMPARATIVE EXAMPLE II

After being melted at about 70 °C, 2.5 g of molten PEG 6000 was added with 1.75 g of aceclofenac, cooled rapidly to room temperature and dried in a freeze-drier for 24 hours or



more. The dried solid dispersed preparation was finely milled in a grinder and passed through a sieve to give a powder which was uniform in particle size.

5

**EXAMPLE XXIV**

In 0.25 g of oleic acid and 0.50 g of Tween 80 was homogeneously mixed and dispersed 1.75 g of aceclofenac, and then, the solution was added in 2.5 g of PEG 6000 which  
10 was molten at about 75 °C. After being cooled rapidly to room temperature  
And dried in a freeze-drier for 24 hours or more, the dried solid dispersed preparation was finely milled in a grinder and passed through a sieve to give a powder which was uniform  
15 in particle size.

**EXAMPLE XXV**

In 0.25 g of cemophor and 0.50 g of Tween 80 was  
20 homogeneously mixed and dispersed 1.75 g of aceclofenac which was, then, added in 2.5 g of PEG 6000 which was molten at about 75 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example XXIV.

25

**EXAMPLE XXVI**

In 0.25 g of labrasol and 0.50 g of Tween 80 was homogeneously mixed and dispersed 1.75 g of aceclofenac which was, then, added in 2.5 g of PEG 6000 molten at about 75 °C. Using this mixture, a dispersed powdery preparation  
5 was obtained in the same procedure as in Example XXIV.

#### EXAMPLE XXVII

In 0.25 g of transcuto1 and 0.50 g of Tween 80 was  
10 homogeneously mixed and dispersed 1.75 g of aceclofenac which was, then, added in 2.5 g of PEG 6000 molten at about 75 °C. Using this mixture, a dispersed powdery preparation was obtained in the same procedure as in Example XXIV.

#### EXAMPLE XXVIII

15

A mixture of 10 g of aceclofenac, 2.5 g of oleic acid, 2.5 g of Tween 80, 5 g of talc and 10 g of PEG 6000 was heated at about 80 °C and homogeneously dispersed in 150 ml of an  
20 alcohol. With the aid of a fluid bed-coating machine (nozzle; 0.8 mm), the resulting solution was sprayed at a rate of 4 ml/min onto 35 g of sugar spheres to give a solid dispersed granule.

#### EXAMPLE XXIX

25

10 g of aceclofenac, 2.5 g of oleic acid, 2.5 g of Tween

80, 3 g of talc, 25 g of Eudragit (Rhompharm, Germany) RS30D  
and 25 g of Eudragit L30D were homogeneously mixed. With  
the aid of a fluid bed-coating machine (nozzle; 0.8 mm), the  
resulting solution was sprayed at a rate of 4 ml/min onto 35  
5 g of the sugar spheres prepared in Example XXVIII.

#### EXAMPLE XXX

10 10 g of aceclofenac, 2.5 g of oleic acid, 2.5 g of Tween  
80, 3 g of talc and 50 g of Eudragit RS30D were homogeneously  
mixed. With the aid of a fluid bed-coating machine (nozzle;  
0.8 mm), the resulting mixture was sprayed at a rate of 4  
ml/min onto the sugar spheres prepared in Example XXVIII.

#### 15 EXAMPLE XXXI

A mixture of 2.5 g of cisapride, 2.5 g of oleic acid,  
2.5 g of Tween 80, 5 g of talc and 23 g of PEG 6000 was heated  
at about 80 °C and added with 150ml of a mixture of acetone  
20 and water (acetone:water, 1:1). With the aid of a fluid  
bed-coating machine (nozzle; 0.8 mm), the resulting mixture  
was sprayed at a rate of 4 ml/min onto 100 g of sugar spheres.

#### EXAMPLE XXXII

25 2.5 g of cisapride, 2.5 g of oleic acid, 2.5 g of Tween  
80, 3 g of talc, 25 g of Eudragit RS30D and 25 g of Eudragit

L30D were homogeneously mixed in 150ml of acetone. With the aid of a fluid bed-coating machine (nozzle; 0.8 mm), the resulting mixture was sprayed at a rate of 4 ml/min onto 70 g of the sugar spheres prepared in Example XXXI.

5

#### EXAMPLE XXXIII

Aceclofenac, lactose, starch and talc were mixed to give a tablet in accordance with the established method.

10 2.5g of aceclofenac, 2.5g of oleic acid, 2.5g of tween 80, 3g of talc, 25g of Eudragit RS30D and 25g of Eudragit L30D were homogeneously mixed. With the aid of a fluid bed-coating machine (nozzle; 0.8mm), the resulting mixture was sprayed at a rate of 4ml/min onto the said tablets to obtain

15 a solid dispersed tablet.

#### EXAMPLE XXXIV

Cisapride, lactose, starch and talc were mixed to give

20 a tablet in accordance with the established method. 2.5g of cisapride, 2.5g of oleic acid, 2.5g of tween 80, 25g of Eudragit RS30D and 25g of Eudragit L30D were homogeneously mixed. With the aid of a fluid bed-coating machine (nozzle; 0.8mm), the resulting mixture was sprayed at a rate

25 of 4ml/min onto the said tablets to obtain a solid dispersed tablet.

**EXPERIMENT I : The Drug Solubility of Solid Dispersed Preparation In Water and Artificial Intestinal Juice**

In this experiment, the solubility of poorly water-soluble drugs in water and artificial intestinal juice was investigated for the solid preparations obtained in Comparative Example and Examples. In this regard, suspensions of 2 g of the solid dispersion preparations of this invention in water or artificial intestinal juice were filtrated through a 0.2  $\mu$ m filter paper (Millipore, Waters, Milford, MA, USA) and the filtrate was diluted for the convenient quantification of the drugs. The solubility results are given in Table 1.

**TABLE 1**

Solubility of Ketoconazole in distilled water and artificial intestinal juice

Solid Dispersed Preparatio	Solubility ( $\mu$ g/mP)	
	DI-Water	Artificial Intestinal Juice
Ketoconazole Powder	0.10	2.08
Comparative Example	3.77	-
Example I	41.4	44.8
Example II	73.9	-
Example III	2.47	-
Example IV	2.28	-
Example V	8.02	-

Example VI	12.0	-
Example VII	6.31	-
Example VIII	12.2	-
Example IX	72.8	50.7
Example X	63.6	37.8

As apparent from the data of Table 1, the solubility of the drugs in distilled water was significantly improved when they were incorporated in solid dispersed preparations containing oleic acid. Particularly, the drugs in the solid dispersed preparations prepared from microemulsions containing oleic acid showed a great advance in the solubility in water as well as in artificial intestinal juice.

10

**EXPERIMENT II: The drug-releasing Rate of Solid Dispersed Preparations in Artificial Gastric and Intestinal Juices**

The solid dispersed preparations comprising ketoconazole or cisapride, respectively, obtained in Examples, were tested for releasing rates in artificial gastric juice and artificial intestinal juice.

According to the paddle process described in Korean Pharmacopoeia VI (KP VI), this releasing test was carried out in artificial gastric juice and artificial intestinal juice at  $37 \pm 0.5$  °C while the paddle was rotated at 50 rpm.

20

At an interval of a predetermined period of time, samples were taken from the artificial juices and filtered through 0.2  $\mu$ m Millipore paper and the filtrates were measured for plasma concentration of drug. The releasing levels and percentages of the poorly water-soluble drugs against artificial gastric and intestinal juices are given in Tables 2 and 3.

TABLE 2

10 Releasing Level ( $\mu$ g/ml) and Percentage (%) of Poorly water-soluble Drugs in Artificial Gastric Juice

Prep.	Time (hours)								
	0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	6.0
Keto. Powder	432 (72.0)	437 (72.8)	436 (72.7)	436 (72.6)	434 (72.4)	439 (73.2)	437 (72.7)	435 (72.5)	437 (72.7)
Exmp. I	46.7 (95.9)	49.4 (101.5)	50.5 (103.8)	50.8 (104.3)	50.8 (104.3)	50.6 (104.1)	50.4 (103.6)	50.5 (103.7)	50.5 (103.8)
Exmp. II	49.5 (108.9)	51.6 (113.5)	52.7 (115.9)	53.1 (116.9)	53.5 (117.7)	53.4 (117.4)	52.9 (116.4)	52.9 (116.4)	53.0 (116.6)
Exmp. III	51.6 (107.5)	51.6 (107.6)	52.7 (109.9)	53.1 (110.8)	53.5 (111.6)	53.8 (112.2)	53.0 (110.6)	53.4 (111.3)	53.0 (110.7)
Exmp. IV	51.7 (112.3)	51.4 (111.8)	51.4 (111.7)	51.2 (111.3)	51.6 (112.2)	52.0 (113.0)	51.5 (111.9)	50.9 (110.6)	51.8 (112.6)
Exmp. V	50.3 (111.5)	50.9 (112.7)	50.4 (111.7)	50.7 (112.3)	50.9 (112.7)	50.8 (112.4)	50.8 (112.4)	60.0 (112.9)	50.7 (112.3)
Exmp. VI	45.8 (99.0)	46.3 (100.0)	46.2 (99.8)	46.2 (99.9)	46.2 (99.9)	45.8 (98.9)	45.6 (98.5)	45.1 (97.5)	45.8 (99.1)
Exmp. VII	48.8 (100.4)	48.8 (100.4)	48.9 (100.4)	48.9 (100.6)	49.0 (100.9)	49.9 (102.5)	49.9 (102.7)	50.2 (103.2)	50.1 (102.9)
Exmp. VIII	46.5 (104.3)	45.8 (102.2)	45.9 (102.9)	45.5 (102.1)	46.4 (104.2)	46.4 (104.1)	45.8 (102.8)	45.3 (101.7)	45.6 (102.3)
Cisa- pride Powder	-	5.249 (51.57)	-	5.492 (54.51)	5.914 (58.63)	6.243 (61.81)	6.173 (61.22)	-	6.446 (65.80)

Exmp. XVII	-	8.83 (85.27)	-	8.74 (84.09)	9.12 (87.9)	8.79 (84.54)	9.13 (87.81)	-	9.30 (89.47)
Exmp. XVIII	-	9.94 (103.2)	-	9.74 (102.1)	10.03 (105.2)	9.93 (104.3)	9.76 (102.4)	-	9.68 (101.5)

As shown in Table 2, ketoconazole, although it can be released in the artificial gastric juice to an extent because of its acidic property, is relatively further improved in the releasing level and percentage when it is incorporated in the oleic acid-containing solid dispersed preparations. Therefore, these data are consistent with those of Experiment I. In the meanwhile, cisapride was released to an extent by virtue of its solubility, but also considerably increased in the releasing properties when it was used in the solid dispersed preparations of the present invention.

TABLE 3

Releasing Level ( $\mu\text{g/ml}$ ) and Percentage (%) of Poorly water-soluble Drugs in Artificial Intestinal Juice

Prep.	Time (hours)								
	0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	6.0
Ketoco azole Powder	1.84 (0.092)	1.89 (0.095)	1.91 (0.096)	1.92 (0.096)	1.94 (0.97)	1.99 (0.099)	1.98 (0.099)	2.05 (0.103)	2.08 0.104
C.Exmp	3.05 (4.99)	3.38 (5.53)	3.69 (6.05)	3.71 (6.08)	3.75 (6.14)	3.84 (6.29)	3.87 (6.33)	3.87 (6.34)	4.32 (7.08)
Exmp. I	4.89 (10.05)	5.14 (10.56)	5.68 (11.67)	5.80 (11.91)	5.17 (10.61)	5.2 (10.68)	5.2 (10.68)	5.32 (10.92)	6.00 (12.33)
Exmp.	3.55	3.61	3.71	3.96	3.7	3.97	4.09	4.11	4.29



II	(7.82)	(7.94)	(8.15)	(8.75)	(8.13)	(8.73)	(8.98)	(9.04)	(9.42)
Exmp. III	1.44 (3.00)	1.45 (3.04)	1.46 (3.05)	1.67 (3.47)	1.77 (3.69)	1.92 (3.99)	1.95 (4.06)	2.14 (4.47)	2.36 (4.92)
Exmp. IV	1.03 (2.23)	1.27 (2.76)	1.31 (2.84)	1.36 (2.95)	1.45 (3.15)	1.48 (3.21)	1.57 (3.41)	1.63 (3.54)	1.69 (3.67)
Exmp. V	2.21 (4.89)	2.23 (4.94)	2.21 (5.03)	2.27 (5.10)	2.31 (5.15)	2.33 (5.46)	2.47 (5.26)	2.38 (5.34)	2.40 (5.30)
Exmp. VI	2.78 (6.00)	2.53 (5.47)	2.42 (5.23)	2.54 (5.49)	2.19 (4.72)	2.41 (5.21)	2.3 (4.97)	2.34 (5.06)	2.45 (5.29)
Exmp. VII	2.09 (4.28)	2.03 (4.16)	2.1 (4.31)	2.20 (4.51)	2.07 (4.26)	2.2 (4.52)	2.16 (4.43)	2.08 (4.26)	2.08 (4.26)
Exmp. VIII	2.26 (5.07)	2.51 (5.61)	2.42 (5.42)	2.64 (5.92)	2.58 (5.77)	2.57 (5.76)	2.42 (5.41)	2.52 (5.64)	2.59 (5.81)
Exmp. IX	3.55 (10.70)	3.95 (11.89)	4.12 (12.41)	4.27 (12.86)	4.28 (12.88)	4.34 (13.08)	4.38 (13.19)	4.38 (13.20)	4.36 (13.13)
Exmp. X	2.37 (6.75)	2.48 (7.05)	2.39 (6.79)	2.14 (6.08)	2.78 (7.92)	2.67 (7.60)	3.42 (9.72)	3.61 (10.27)	3.63 (10.33)
Cisa- pride Powder	-	0 (0)	-	0 (0)	0 (0)	0 (0)	0.005 (0.047)	0.028 (0.27)	0.0745 (0.618)
Exmp. XVII	-	2.43 (20.15)	-	3.22 (26.7)	2.70 (22.42)	2.66 (22.1)	2.64 (21.94)	3.10 (25.73)	3.99 (33.12)
Exmp. XVIII	-	6.34 (63.0)	-	6.75 (67.01)	6.56 (65.15)	6.55 (65.05)	6.69 (66.46)	6.74 (66.9)	6.96 (69.05)

The effect of the solid dispersed preparations on improving the releasing rates of the two drugs is more apparent in the artificial intestinal juice, a more  
5 difficult condition in which for the two drugs to dissolve.

As shown in Table 3, the releasing properties of drugs are better when they are incorporated in the solid dispersed preparations using fatty acid and oil than when they are used alone. A better improvement effect was obtained from  
10 the solid dispersed preparations containing oleic acid.

Further, the use of microemulsified oleic acid brought

about a great advance in the releasing properties.

In addition, the solid dispersed preparations containing itraconazole, its derivatives, and cyclosporine, respectively, was tested for the releasing properties in the artificial gastric and intestinal juices. The results are given in Table 4. Also, the data of Table 4 demonstrate that the drugs in the solid dispersed preparations are superior to the drugs alone in the releasing properties.

10

TABLE 4

Releasing Level ( $\mu\text{g/ml}$ ) of Poorly water-soluble Drugs in Artificial Gastric and Intestinal Juice

Prep.	Time (Min)											
	Artificial Gastric Juice						Artificial Intestinal Juice					
	5	15	30	60	90	120	5	15	30	60	90	120
Itra <sup>1</sup>	14.4	16.4	17.4	16.7			0.05	0.05	0.05	0.05	-	-
Exmp.XII	292	293	321	331			130	95.0	146	102	-	-
Exmp.XIII	138	160	179	192			246	214	204	203	-	-
Itra Drv. <sup>2</sup>	96.9	156.2	189.2	211.0	216.7		-	-	-	-	-	-
Exmp.XIV	204.5	198.6	232.6	252.9	259.8		-	-	-	-	-	-
Cyclo. <sup>3</sup>	-	-	1.8	1.7	-	1.9	-	-	2.1	2.3	-	2.5
Exmp.XV	-	-	111.4	94.8	-	71.7	-	-	102.8	99.4	-	91.0
Exmp.XVI	-	-	11.1	10.8	-	9.8			595.0	66.3	-	56.7

<sup>1</sup> Itrakonazole powder

<sup>2</sup> Itrakonazole derivative

15 <sup>3</sup> Cyclosporine

EXPERIMENT III: Uptake of Poorly water-soluble Drugs in

### Rabbit 's Gastrointestinal tract

The solid dispersed preparations containing ketoconazole, prepared from Examples, were tested for the uptake in rabbit's gastrointestinal tract. The results are given in Table 5.

In this regard, first, a rabbit was killed by introducing air in its ear vein and its stomach, duodenum, jejunum, ileum, colon and rectum were excised and washed with physiological saline solution at 37 °C. These organs were fixed between the receptor and donor of a Franz diffusion cell. In the receptor, a physiological saline solution warmed to 37 °C was poured, and stirred with a magnetic stirrer while the solid dispersed preparations obtained in Examples were added in the donor. Samples were harvested from the receptor at predetermined times for 6 hours while the receptor was supplemented with a fresh physiological saline solution in order to constantly maintain the total volume in the receptor. The samples taken were measured for their plasma concentrations of drugs.

**TABLE 5**

Uptake ( $\mu\text{g}/\text{cm}^2$ ) of Ketoconazole in Rabbit's GI tract

Prep.	Time (hours)							
	0.3	0.67	1	1.5	2	3	4	6
C. Exmp	0	0.92	2.45	4.50	4.67	5.15	5.56	5.95

Exmp. I	0	1.72	3.44	5.46	9.10	10.2	11.6	13.2
Exmp. II	0.50	2.78	5.50	9.83	15.5	16.3	18.6	22.4

It is apparent from the data of Table 5 that the uptake of the drug in the GI tract is much better when it is incorporated in the solid dispersed preparation using oleic acid than when it is incorporated in the conventional dispersed preparation which uses a water-soluble matrix merely. Particularly, a significant improvement in the uptake of ketoconazole in the GI tract was brought about by the use of the solid dispersed preparations obtained from microemulsions containing oleic acid. These results are consistent with those of Experiment I and II.

**EXPERIMENT IV: Comparison of the Plasma Concentration of Drugs Formulated into a Solid Dispersed Preparation and Commercially Available Ones**

Before an experiment, male mice (Sprague-Dawley lineage) weighing 250-310 g, purchased from the Korea National Institute of Health, were adapted to new circumstances for 1-2 weeks. After the mice, which were starved from one day before the experiment, were etherized, their left femoral arteries were inserted with cannulas connected to syringes containing 80 IU/ml of heparin. After 2 hours, the mice came out of the ether and were administered with a suspension of the cyclosporine-

containing solid dispersed preparation of the present invention and a commercially available preparation with the aid of a sonde. At an interval of a predetermined period of time, blood was taken from the left femoral arteries and  
5 measured for the plasma concentration of drug.

With reference to Fig. 1, the cyclosporine level in blood are plotted against the times after administration for the solid dispersed preparations of the present invention and a commercially available preparation. As  
10 shown in the graph, the plasma concentration of the solid dispersed preparations according to the present invention are similar to that of the commercially available preparation, Neoral. Although being a little bit lower concentration than that of Neoral as a whole, the solid  
15 dispersed preparations according to the present invention are thought to have the initiatives to substitute for the conventional preparations which contain liquid drugs, in a pharmaceutical aspect.

Solid dispersed preparations according to the present  
20 invention and a commercial available preparation, all containing itraconazole as a medicinally effective ingredient, were administered to beagle dogs in an oral route. After a blood sample was taken from their veins at an interval of a predetermined period of time, the plasma  
25 concentration of drug was measured. The results are given in Table 6.

TABLE 6

Itraconazole Level ( $\mu\text{g/ml}$ ) in Blood According to Times

Prep.		Time (hours)							
		1	2	3	4	6	8	10	24
Starved Dog	Exmp. XII	0	0.03	0.03	0.04	0.03	0.02	0.02	0.02
	Exmp. XIII	0.02	0.06	0.07	0.08	0.10	0.07	0.04	0.03
	Purchased	0	0.06	0.04	0.03	0.09	0.03	0.06	0.03
Non-starved	Exmp. XIII	0.12	0.41	0.38	0.44	0.43	0.43	0.42	0.36
	Purchased	0.30	0.60	0.79	0.58	0.54	0.44	0.41	0.30

As apparent from Table 6, a similar pharmacokinetic pattern was observed between the plasma concentration of itraconazole from the solid dispersed preparations and from the conventional preparation (itazol) when starved beagle dogs were administered therewith, while the lower value shown in case the preparation of Examp. XII was administered. In non-starved beagle dogs, the drug reached a high maximal level in blood within a fast period of time when the commercially available preparation was administered whereas the preparation of Example XIII maintained the plasma concentration of drug constantly, owing to its solubilization in the gastro-intestinal tract.

#### EXPERIMENT V: Solubility of Aceclofenac in Various Vehicles

Excess aceclofenac was added in 5 ml of a vehicle in a test tube, which was then vortexed to an extent that the drug

was not dissolved further, and incubated for 3 days in a 37 °C water bath. The resulting solution was filtrated through a 0.2 µm filter paper (Millipore, Waters, Milford, MA, USA) and the filtrate was diluted for the convenient quantification of the drug. The solubility results are given in Table 7.

**Table 7**

Solubility of Aceclofenac in Vehicles

Vehicles	Solubility (mg/mP)
Transcutol	149.34
Labrasol	114.83
Tween 80	98.70
Tween 20	85.71
Cremophor EL	40.92
Cremophor RH40	23.34
Oleic acid	4.59
Linoleic acid	5.44
Triacetin	18.01
Castor oil	13.21
Sesame oil	2.83
Corn oil	2.20
Mineral oil	0.34

10

As apparent from the data of Table 7, large values are found in the solubility of aceclofenac in fatty acids, triacetin, castor oil and cremophor. Particularly, the drug is dissolved at great amounts in transcutol, labrasol and Tweens.

15

#### EXPERIMENT VI: Releasing of Aceclofenac in Solid Dispersed Preparations Against Artificial Gastric and Intestinal

## Juices

The solid dispersed preparations comprising aceclofenac, obtained in Examples XXIV to XXVII, were tested for releasing properties against artificial gastric juice and artificial intestinal juice in a similar manner to that of Experimental Example II.

The releasing levels and percentages of the poorly water-soluble drugs against artificial gastric and intestinal juices are given in Tables 8 and 9.

**Table 8**  
Releasing Level ( $\mu\text{g/ml}$ ) and Percentage (%) of  
Aceclofenac in Artificial Gastric Juice

Prep.	Time (hours)						
	0.25	0.5	0.75	1.0	1.5	2.0	3.0
Aceclofenac Powder	0.46 (0.23)	0.53 (0.26)	0.57 (0.28)	0.60 (0.30)	0.61 (0.31)	0.69 (0.34)	0.73 (0.37)
Exmp. XXIV	1.01 (0.51)	1.16 (0.58)	1.29 (0.65)	1.33 (0.67)	1.35 (0.67)	1.43 (0.72)	1.38 (0.69)
Exmp. XXV	1.68 (0.84)	2.38 (1.19)	2.43 (1.22)	2.51 (1.25)	2.68 (1.34)	2.65 (1.33)	2.70 (1.35)
Exmp. XXVI	1.61 (0.80)	1.88 (0.94)	1.96 (0.98)	1.98 (0.99)	1.99 (1.10)	1.95 (0.98)	2.08 (1.04)
Exmp. XXVII	1.76 (0.88)	2.04 (1.02)	2.36 (1.18)	2.51 (1.26)	2.61 (1.30)	2.70 (1.35)	2.63 (1.31)
Airtal	0.93 (0.46)	1.02 (0.51)	1.18 (0.59)	1.23 (0.61)	1.32 (0.66)	1.34 (0.67)	1.39 (0.70)

15

As shown in Table 8, the releasing of aceclofenac in the artificial gastric juice was much improved when it was



in the solid dispersed preparations of the present invention relatively to the other preparations.

TABLE 9

5           Releasing Level ( $\mu\text{g/ml}$ ) and Percentage (%) of  
           Aceclofenac in Artificial Intestinal Juice

Prep.	Time (hours)							
	0.25	0.5	0.75	1.0	1.5	2.0	3.0	5.0
Aceclo. Powder	88.37 (44.19)	117.34 (58.67)	121.65 60.82	126.64 (63.32)	128.10 (64.05)	131.70 (65.85)	136.55 (68.27)	136.55 (68.28)
Exmp. XXIV	152.97 (76.49)	157.43 (78.72)	161.90 80.95	160.40 (80.20)	162.66 (81.33)	164.09 (82.05)	165.27 (82.63)	166.71 (83.35)
Exmp. XXV	151.72 (75.86)	163.33 (81.67)	161.72 80.86	163.11 (81.55)	162.26 (81.13)	165.57 (82.79)	166.16 (83.08)	166.16 (83.08)
Exmp. XXVI	148.21 (74.10)	152.40 (76.20)	154.58 77.29	154.95 (77.47)	154.49 (77.24)	155.48 (77.74)	157.97 (78.99)	159.74 (79.87)
Exmp. XXVII	138.83 (69.41)	150.41 (75.21)	155.85 77.92	161.51 (80.75)	161.63 (80.81)	163.29 (81.64)	164.22 (82.11)	167.36 (83.68)
Airtal	133.76 (66.88)	136.54 (68.27)	136.62 68.31	137.70 (68.85)	142.55 (71.28)	145.72 (72.86)	143.66 (71.83)	142.34 (71.17)

As known from Table 9, aceclofenac, although it can be released in the artificial gastric juice to an extent  
 10 because of its basic property, is relatively further improved in the releasing level and percentage when it is formulated into the solid dispersed preparation.

EXPERIMENT VII: Comparison of Plasma Concentration of  
 15 Aceclofenac Between Solid Dispersed Preparation and Conventional Ones

Before an experiment, male mice (Sprague-Dawley lineage) weighing 250-310 g, purchased from the Korea National Institute of Health, were adapted to new circumstances for 1-2 weeks. After the mice, which were  
5 starved from one day before the experiment, were etherized, their left femoral arteries were inserted with cannulas connected to syringes containing 50 IU/ml of heparin. After 2 hours, the mice came out of the ether and were administered with a suspension of the aceclofenac-  
10 containing solid dispersed preparation of the present invention and a aceclofenac powder with the aid of a sonde. At an interval of a predetermined period of time, blood was taken from the left femoral arteries and measured for the plasma concentration of the drug.

15 In the meanwhile, the aceclofenac-carrying solid dispersed preparations of the present invention and a commercial available preparation were orally administered to beagle dogs and volunteers. At predetermined times after oral administration, blood was taken from the beagle  
20 dogs and the volunteers and measured for the drug levels.

After the oral administration of the aceclofenac-carrying solid dispersed preparations of the present invention, an aceclofenac powder and a commercial available preparation to mice, beagles dogs and volunteers, the  
25 plasma concentration of the drug with time were compared and are plotted in Figs. 2 to 4.

As shown in the graphs, the solid dispersed preparations of

the present invention maintain higher levels of aceclofenac in blood for all of the testees than the commercially available preparation. In addition, the use of the solid dispersed preparation according to the present invention was affirmed to increase the maximal value of plasma concentration and area under the curve, which are pharmacokinetic parameters, by 1.5-6 times.

After the oral administration of the aceclofenac-carrying solid dispersed preparation of the present invention, a commercially available preparation and an aceclofenac powder, the plasma concentration of aceclofenac was monitored with time and the results are given in Tables 10 to 12, below.

TABLE 10

Aceclofenac Level ( $\mu\text{g/ml}$ ) in Blood of Rat

Prep.	Time (hours)								
	0.25	0.5	0.75	1	1.5	2	3	4	6
Exmp. XXIV	11.11	14.30	12.96	8.01	4.45	3.38	2.60	0.70	0.85
Aceclo. Powder	1.85	0.71	0.44	0.15	0.03	0.16	0.21	0.27	0.13

It is apparent from the data of Table 10 that the aceclofenac level in blood is significantly improved when the drug is administered by use of the preparation of the present invention relative to when aceclofenac is administered alone.

TABLE 11

Plasma Concentration ( $\mu\text{g/ml}$ ) of Aceclofenac  
in Beagle Dogs

Prep.	Time (hours)											
	0.25	0.5	0.75	1	1.5	2	3	5	7	9	12	24
Exmp. XXIV	4.9	41.1	74.1	81.8	93.0	96.5	71.1	49.4	32.2	21.6	11.1	1.3
Airtal	4.6	15.1	28.9	35.7	50.8	43.2	31.9	16.6	8.8	6.4	3.9	0.8

The data of Table 11 demonstrate that the  
5 aceclofenac-carrying solid dispersed preparation of the  
present invention is superior to the conventional  
preparation in the plasma concentration.

TABLE 12

10 Plasma Concentration ( $\mu\text{g/ml}$ ) of Aceclofenac  
in Human Blood

Prep.	Time (hours)										
	0.25	0.5	0.75	1	1.5	2	3	5	7	9	12
Exmp. XXIV	0.16	4.67	10.98	18.12	12.99	6.93	2.97	1.02	0.67	0.56	0.42
Airtal 1	0.85	1.75	3.84	5.51	5.48	8.34	3.44	0.48	0.29	0.14	0.10

As apparent from the data of Table 12, higher levels of  
aceclofenac in blood are maintained when the solid  
15 dispersed preparation of the present invention is  
administered than when the commercially available  
preparation is used.

EXPERIMENT VIII: Releasing of Cisapride From Solid

### Dispersed Preparations Against Artificial Gastric and Intestinal Juices

The solid dispersed preparation comprising cisapride, obtained in Examples XXXI, was tested for releasing properties against artificial gastric juice and artificial intestinal juice in a similar manner to that of Experimental Example II.

The releasing levels and percentages of the poorly water-soluble drugs against artificial gastric and intestinal juices are given in Table 13.

**TABLE 13**

Releasing Level ( $\mu\text{g/ml}$ ) and Percentage (%) of Cisapride in Artificial Gastric and Intestinal Juice

Juice	Time (hour)									
	0.5	1.0	1.5	2.0	3.0	4	5	6	8	12
Gastric	14.9	26.2	32.0	43.4	58.5	-	84.7	-	-	-
Intestina	8.1	16.5	25.2	38.1	48.5	62.1	-	72.7	87.8	98.0

The amount of the drug released from the solid dispersed preparation was increased almost linearly in both artificial gastric and intestinal juices, showing a zero order-like kinetics.

#### EXPERIMENT IX: Comparison of Plasma Concentration of

# Cisapride Between Solid Dispersed Preparation and Commercially Available Ones

At an interval of a predetermined period of time after  
5 the oral administration of beagle dogs with the  
cisapride-carrying solid dispersed preparation obtained in  
Example XXXII and a commercially available preparation,  
blood was taken from the testees and measured for plasma  
concentration of drug.

10 With reference to Fig. 5, the cisapride levels in blood are  
plotted against the times after administration for the  
solid dispersed preparations of the present invention and a  
commercially available preparation, Prepulsid tablet. As  
shown in the graph, the plasma concentration of the solid  
15 dispersed preparations according to the present invention  
are greatly improved relative to that of the commercially  
available preparation. These drug concentrations are  
numerically shown in Table 14, below.

20

TABLE 14

Plasma Concentration of Cisapride ( $\mu\text{g/ml}$ )  
in Beagle Dog

Prep.	Time (hours)											
	0.5	0.75	1	1.25	1.5	2	3	5	7	9	12	24
Exmp. XXXII	48	80	68	82	97	151	271	284	152	104	83	63
Prepulsid	49	61	70	83	102	184	201	134	75	58	46	41

As shown in Table 14, the plasma concentration of cisapride is maintained at higher levels when the solid dispersed preparation of the present invention is used than when the conventional preparation.

5

As described hereinbefore, the solid dispersed preparations of the present invention are improved in the solubility of poorly water-soluble drugs in the gastrointestinal tract, in detail, the releasing of the drugs against the gastric and intestinal juices, resulting in a great increase in the bioavailability of the drugs. In addition, the solid dispersed preparations of the present invention give the pharmaceutical solutions to the problems that the conventional semi-solid or liquid preparations possess, enabling medicinally effective, poorly water-soluble compounds to be formulated, molded and processed, quickly and in an economically favorable manner without use of any organic solvent.

The present invention has been described in an illustrative manner, and it is to be understood the terminology used is intended to be in the nature of description rather than of limitation. Many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described.

## WHAT IS CLAIMED IS:

1. A solid dispersed preparation for poorly water-soluble drugs, prepared by dissolving or dispersing the drugs in an oil, a fatty acid or a mixture thereof, mixing the solution or dispersion in a water-soluble polyol matrix and drying the mixture.
2. The solid dispersed preparation as set forth in claim 1, wherein the solid dispersed preparation is obtained by pulverizing the dried mixture to give a dispersed powdery preparation.
3. The solid dispersed preparation as set forth in claim 1, wherein the mixture is dried in such a way that the mixture is sprayed to pharmaceutically acceptable nuclei to give a dispersed granular preparation.
4. The solid dispersed preparation as set forth in claim 1, wherein the oil, the fatty acid or the mixture thereof is used in a form of an emulsion or a micro emulsion.
5. The solid dispersed preparation as set forth in claim 1, wherein the oil is selected from the group comprising  $\alpha$ -bisabolol, stearyl glycerethinate, salicylic acid, tocopheryl acetate, sodium hyaluronate, panthenol, propylene glycol and apple (*Pirus Malus*), propylene



glycol and pineapple, ivy (*Hedera helix*) extract and  
1,3-B.G, peach (*Prunus persica*) leaf extract, hydrolyzed  
soy flour, wheat (*Triticum Vulgare*) protein, birch  
(*Betula alba*) extract and 1,3-B.G, burdock (*Arctium*  
5 *majus*) extract and 1,3-B.G, liposomes,  
phosphatidylcholines, glyceryl stearate,  
captylic/capric triglyceride, cetyl octanoate,  
isopropyl myristate, 2-ethylene isopelagonate, di-C12-  
13 alkyl malate, cetearyl octanoate, butylene glycol  
10 dicaprylate/dicaprate, isononyl isostearate,  
isostearyl isostearate, coco-caprylate/caprate, cetyl  
octanoate, octyldodecyl myristate, cetyl esters, C10-30  
cholesterol/lanosterol ester, hydrogenated castor oil,  
monoglycerides, diglycerides, triglycerides, beeswax,  
15 canauba wax, sucrose distearate, PEG-8 beeswax, ceresin,  
ozokerite, macadamia ternifolia nut oil, hydrogenated  
hi-erucic acid rape seed oil, olive oil, jojoba oil,  
hybridsunflower (*Helianthus annuus*) oil, and dog rose  
(*rosa canina*) lips oil.

20

6. The solid dispersed preparation as set forth in claim  
5, wherein the oil is selected from the group comprising  
mineral oils, squalene, squalane, monoglycerides,  
diglycerides, triglycerides, medium chain glycerides,  
25 myglyol, cremophor, hydrogenated castor oil, corn oil,  
perilla oil, cotton seed oil and lipid-soluble vitamins.

7. The solid dispersed preparation as set forth in claim 1, wherein the fatty acid is selected from the group comprising oleic acid, cetyl alcohol, stearyl alcohol, stearic acid, myristic acid, linoleic acid and lauric acid.
8. The solid dispersed preparation as set forth in claim 7, wherein the fatty acid is selected from the group comprising oleic acid, linoleic acid, and isopropyl myristate.
9. The solid dispersed preparation as set forth in claim 1, wherein the water-soluble polymer matrix is selected from the group comprising polyethylene glycol (PEG), carbowax and polyvinyl pyrrolidone (PVP).
10. The solid dispersed preparation as set forth in claim 1, wherein the poorly water-soluble drugs are dissolved and dispersed in the oil, fatty acid or their mixture in the presence of a surfactant.
11. The solid dispersed preparation as set forth in claim 10, wherein the surfactant is selected from the group comprising glyceryl stearate, polysorbate 60, polysorbate 80, sorbitan trioleate, sorbitan sesquioleate, sorbitan stearate, PEG-20 glyceryl isostearate, ceteth-25, PEG-60, PEG-60 hydrogenated

castor oil, nonoxynol-15, PEG-6-decyltetradeceth-20,  
dimethicone copolyol, glyceryl diisostearate, ceteth-  
24, cetearyl alcohol, polyoxyethylene nonyphenyl ether,  
PEG-40 hydrogenated castor oil, cetyl dimethicone  
5 copolyol, polyglyceryl-3-methylglucose distearate,  
PEG-100 stearate, sorbitan isostearate, sodium lauryl  
glutamate, disodium cocoamphodiacetate, lauric acid  
diethanolamide, coconut fatty acid diethanolamide,  
N,N-bis-(2-hydroxy ethyl)-cocamide, and  
10 cocoamidopropyl betain.

12. The solid dispersed preparation as set forth in claim  
1, wherein the water-soluble polymeric matrix is used  
alone or in combination with other water-soluble  
15 matrices.

13. The solid dispersed preparation as set forth in claim  
12, wherein the other water-soluble matrix is selected  
from the group comprising gelatin, gum, carbohydrates,  
20 celluloses, polyvinyl alcohol, polyacrylic acid,  
inorganic compounds and their mixtures,  
hydroxypropylmethylcellulose acetyl succinate, shellac,  
zein, polyvinyl acetate phthalate, Eudragit L100,  
Eudragit S100, sodium arginate, and poly-L-lysine.

25

14. The solid dispersed preparation as set forth in claim  
1, wherein the poorly water-soluble drugs are selected

from the group comprising ketoconazole, itraconazole  
and its derivatives, cyclosporine, cisapride,  
acetaminophen, aspirin, acetylsalicylic acid,  
indomethacin, naproxen, warfarin, papaverine,  
5 thiabendazole, miconazole, cinnarizine, doxorubicin,  
omeprazole, cholecalciferol, melphalan, nifedipine,  
digoxin, benzoic acid, tryptophan, tyrosine,  
phenylalanine, aztreonam, ibuprofen,  
phenoxymethylpenicillin, thalidomide,  
10 methyltestosterone, prochlorperazine, hydrocortisone,  
dideoxypurine nucleoside, vitamin D<sub>2</sub>, sulfonamide,  
sulfonylurea, p-aminobenzoic acid, melatonin,  
benzylpenicillin, chlorambucil, diazepam, digitoxin,  
hydrocortisone butyrate, metronidazole benzoate,  
15 tolbutamide, prostaglandin E<sub>1</sub> (PGE<sub>1</sub>), fludrocortisone,  
griseofulvin, miconazole nitrate, leukotriene B<sub>4</sub>  
antagonist, propranolol, theophylline, flubiprofen,  
sodium benzoate, benzoic acid, riboflavin,  
benzodiazepine, phenobarbital, glyburide, sulfadiazine,  
20 sulfaethylthiadiazole, sodium diclofenac, aceclofenac,  
pheniramine, hioridazinehydrochloride, bropiramine,  
hydrochlorothiazide, fluconazole, acyclovir,  
bucillamine, ciprofluoxacin, acetyl-L-carnitine,  
baclofen, sodium alendronate, lovocarnitine,  
25 nimodipine or nimodifine, atenolol, provastatin sodium,  
lovastatin, isotretinoin, etidronate disodium,  
doxifluridine, fosfomycin calcium, sotepine,

epinastine hydrochloride, carvedilol, epinastine  
hydrochloride, carvedilol, fosinopril, trandolapril,  
etretinate cap, metergoline, mercaptopurine,  
vancomycin hydrochloride, cefixime, cefuroxim axetil,  
5 dirithramycin, and dadanosin.

15. The solid dispersed preparation as set forth in claim  
13, wherein the poorly water-soluble drugs are selected  
from the group comprising ketoconazole, itraconazole  
10 and its derivatives, cisapride, cyclosporine,  
nifedipine and aceclofenac.

16. Medicines for internal use such as powders, granules,  
tablets and capsules, prepared using the solid dispersed  
15 preparation of claim 1.

FIG. 1

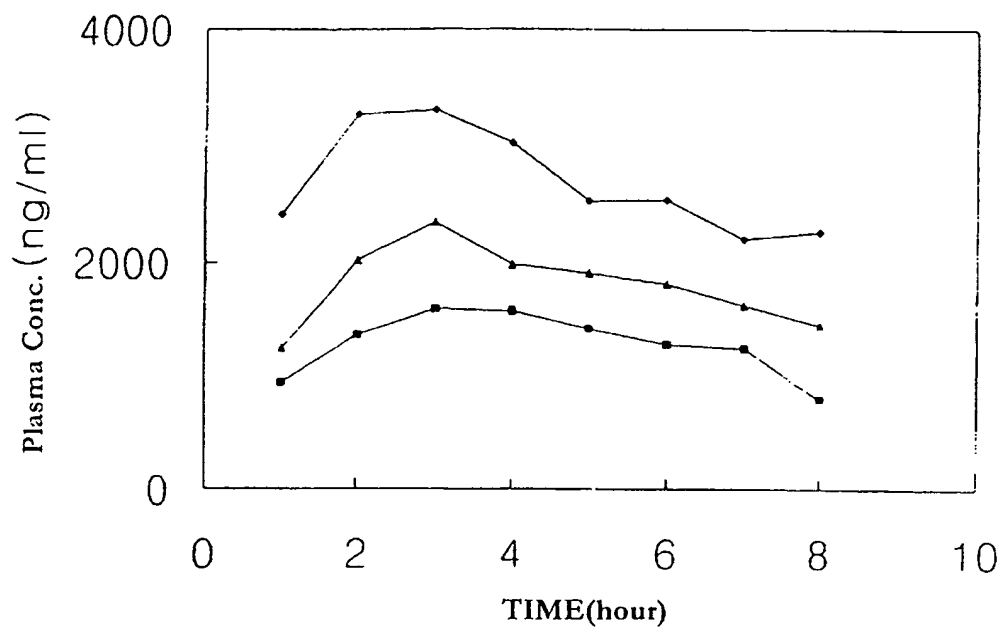


FIG. 2

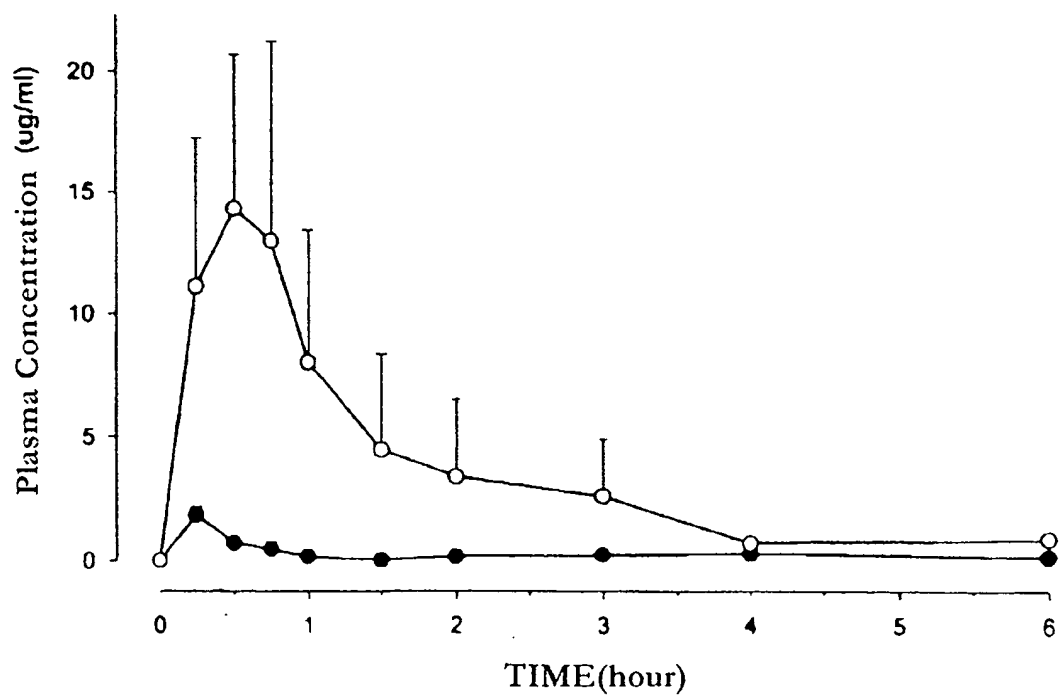


FIG. 3

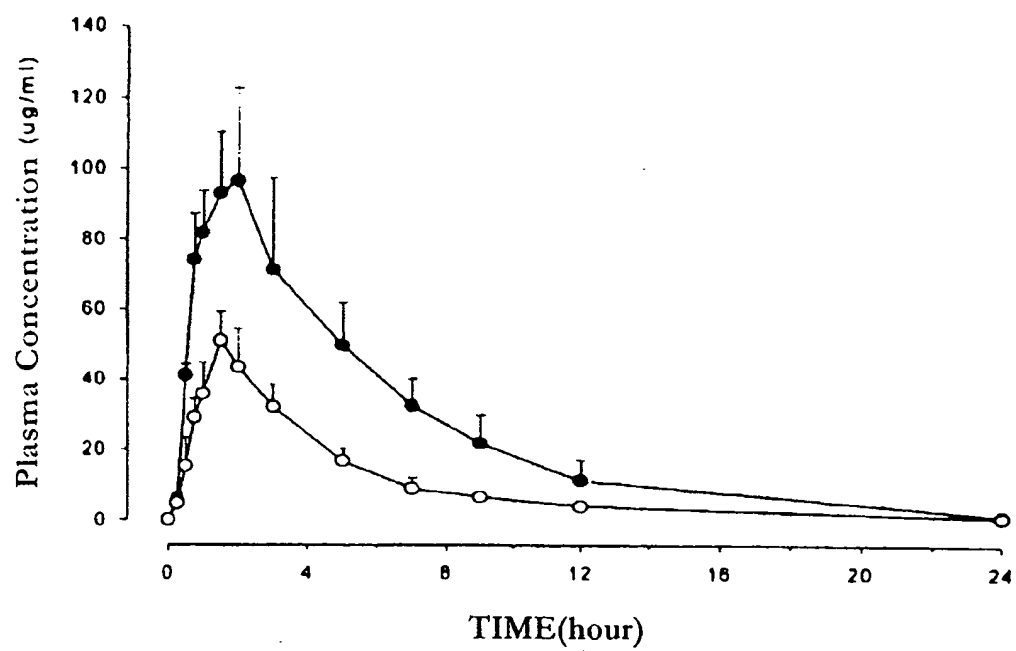


FIG. 4

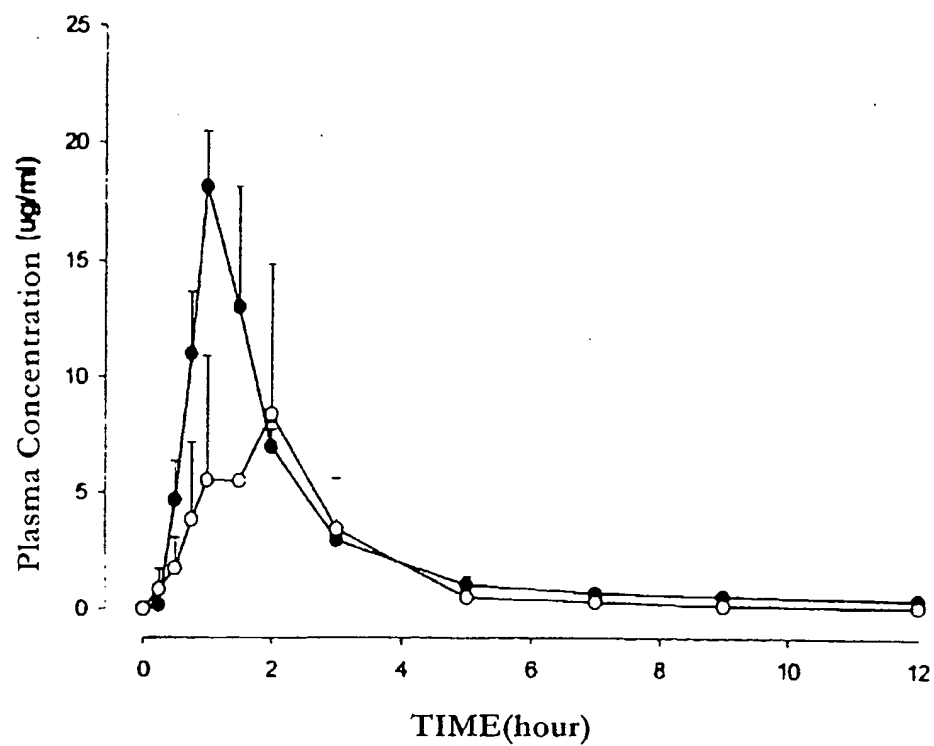
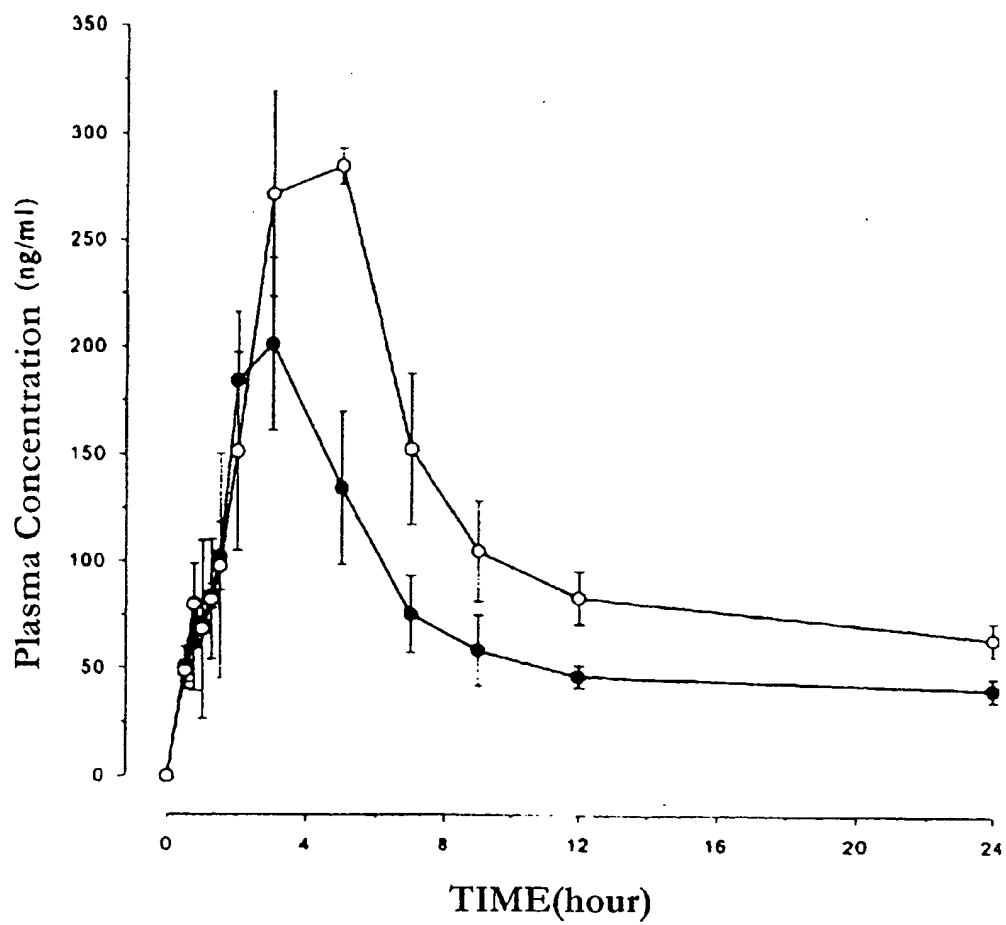




FIG. 5



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR 99/00341

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC <sup>6</sup> : A 61 K 9/14, A 61 K 9/16, A 61 K 9/20, A 61 K 9/48, A 61 K 31/20, A 61 K 9/107, A 61 K 38/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC <sup>6</sup> : A 61 K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
WPI		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9006746 A1 (MEDICONTROL CORPORATION) 28 June 1990 (28.06.90) abstract; page 5, 2 <sup>nd</sup> paragraph; page 6, 1 <sup>st</sup> paragraph; claims 1-6,8,10-12,15,16,18,22,24,25,27.	1,2,4-6,10-14,16
X	US 5756450 A (HAHN et al.) 26 May 1998 (26.05.98) abstract; column 4, lines 33-40, 46-54; column 7, lines 33-51; column 9, lines 36-40; column 14, lines 30-60; column 19, lines 3-47.	1,2,4-6,9,12-16
X	JP 08-157362 A (SANKYO CO LTD) 18 June 1996 (18.06.96) (abstract) [online] [retrieved on 28 October 1999 (28.10.99)]. Retrieved from the Internet:<URL: <a href="http://12.espacenet.com/dips/viewer?PN=JP8157362&amp;CY=at&amp;LG=de&amp;DB=EPD">http://12.espacenet.com/dips/viewer?PN=JP8157362&amp;CY=at&amp;LG=de&amp;DB=EPD</a> >.	1-4,10,12,16
----		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: „A“ document defining the general state of the art which is not considered to be of particular relevance „E“ earlier application or patent but published on or after the international filing date „L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) „O“ document referring to an oral disclosure, use, exhibition or other means „P“ document published prior to the international filing date but later than the priority date claimed „T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention „X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone „Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art „&“ document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
28 October 1999 (28.10.99)		03 December 1999 (03.12.99)
Name and mailing address of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200		Authorized officer  Krenn  Telephone No. 1/53424/435

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 99/00341

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